REMARKS

In view of the following remarks, the Examiner is requested to allow claims 1, 3-8, 10, 12-13, 19-24, 30, 32-33 and 36-39, the only claims pending and under examination in this application. Claims 2, 9, 25-29 and 34-35 are canceled. Claims 11, and 14-18 are withdrawn from consideration.

Claims 1, 3, 8, 10, 19, 20, 22, 23-24, 30, 32, 33, and 36-39 have been amended. Claim 1 has been amended to incorporate the elements of Claim 2. Claim 8 has been amended to incorporate the elements of Claim 9. Consequently, Claims 2 and 9 have been canceled. Claims 19, 20, 22, 23 and 30 have been amended to indicate that the antiproliferative agent is a HMG-CoA reductase inhibitor, as recited in Claim 1. Claims 33 and 37-38 have been amended to specifically recite the use of simvastatin in the methods of the invention. Claims 3 and 10 have been amended to correct their dependency. Accordingly, no new matter has been added.

As no new matter has been added by way of this/these amendment(s), entry thereof by the Examiner is respectfully requested.

Claim Rejections - 35 U.S.C. § 112, first paragraph

Claims 1, 4-10, 12-13 and 19-24 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled for the full scope of the invention.

The Applicants respectfully disagree. However, solely in order to expedite prosecution and advance the case to issuance the Applicants have amended the claims. These amendments should not be construed as acquiescence to any position of the Office. Independent Claim 1 has been amended to specifically recite the use of an HMG-CoA reductase inhibitor, and lists the specific lung proliferative diseases set forth in originally filed Claim 2. Further, Claims 33 and 37-38 have been amended to specifically recite the use of simvastatin in the methods of the invention.

In view of the above amendments and remarks, withdrawal of the rejection is requested.

Claim Rejections - 35 U.S.C. § 112, second paragraph

Claims 1-10 12-13 and 19-24 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

According to the M.P.E.P. § 2173.02, in reviewing a claim for compliance with 35 U.S.C. 112, second paragraph, the examiner must consider the claim as a whole to determine whether

the claim apprises one of ordinary skill in the art of its scope and, therefore, serves the notice function required by 35 U.S.C. 112, second paragraph, by providing clear warning to others as to what constitutes infringement of the patent.

The Office asserts that Claim 1's recitation of "which does not substantially increase endothelial cell nitric oxide synthase activity in the endothelial cells of the pulmonary arteries of the patient," renders the claims indefinite. The Office asserts that the specification does not provide a standard for this element and that one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

The Applicants, however, disagree. At page 10, lines 2 to 6 of the specification, the Applicants teach that:

> "The term 'which does not substantially increase endothelial cell nitric oxide synthase activity in the endothelial cells of the pulmonary arteries of the patient' refers to an increase of NOS expression or activity to levels which would exist in normal healthy endothelial tissue, but not to any enhancement of NOS expression or activity above levels that would exist in normal healthy endothelial tissue."

The Applicants contend that it is well within the skill set of an ordinary practitioner to determine the NOS expression levels that are exhibited by normal healthy endothelial tissues. Such methods are well known in the art and routinely practiced. For instance, Example 5 clearly teaches how endothelial cell NOS expression levels can be measured in healthy tissue and compared to levels within diseased tissue.

Therefore, in view of the teachings of the specification, one of ordinary skill in the art, using routine methods, could determine normal NOS expression levels in healthy endothelial tissue and would clearly understand what would constitute an enhancement of said expression levels above that which exist in the healthy tissue. Accordingly, the Applicants contend that the "metes and bounds" of the claims would be clear to one of skill in the art and respectfully request that this rejection be withdrawn.

Claim Rejections - 35 U.S.C. § 102

Claims 1-7, 19-22, 30-31, 33-36 and 38 have been rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Nishimura et al. (American Journal of Respiratory and Critical Care Medicine, Vol. 166, 2002, pp. 1403-1408). Applicants respectfully traverse the rejection.

The M.P.E.P. § 706.02(b) states that a rejection based on a 35 U.S.C. § 102(a) rejection may be overcome by filing a declaration under 37 C.F.R. 35 U.S.C. § 1.132 showing that the cited anticipatory reference is not by "another." Accordingly, filed herewith is a § 1.132 declaration establishing the fact that the cited reference is, in fact, the work of the present inventors.

Therefore, in view of the 1.132 declaration, filed herewith, this rejection may be withdrawn.

Claims 1-10, 12, 19-22, 30-36 and 38-39 have been rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Liao et al. (WO 00/56403).

According to the M.P.E.P., a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. The identical invention must be shown in as complete detail as is contained in the claim. See M.P.E.P. § 2131.

Claim 1 is directed to a method of treating a lung proliferative vascular disorder in a patient by administering an HMG-CoA reductase inhibitor. The HMG-CoA reductase inhibitor is present in an amount effective to reduce vascular occlusion in the pulmonary arteries of the patient, however, it does not substantially increase endothelial cell nitric oxide synthase activity in the endothelial cells of the pulmonary arteries of the patient. Additionally, the lung proliferative vascular disorder is selected from the group consisting of primary pulmonary hypertension, secondary pulmonary hypertension, Eisenmenger's syndrome, chronic thromboembolic disease, pulmonary fibrosis, obliterative bronchiolitis, and lymphangioleiomyomatosis.

Accordingly, an element of the claims is administering an amount of a HMG-CoA reductase inhibitor that is effective to reduce vascular occlusion in the pulmonary arteries but does not substantially increase endothelial cell nitric oxide synthase activity in the endothelial cells of the pulmonary arteries. The Applicants contend that Liao does not teach this element. Liao does not teach this element because Liao actually teaches the increase of endothelial cell nitric oxide synthase activity. See for instance, page 4, lines 21 to 26, below:

> According to one aspect of the invention, a method is provided for increasing endothelial cell Nitric Oxide Synthase activity in a nonhypercholesterolemic subject who would benefit from increased endothelial cell Nitric Oxide Synthase activity in a tissue. The method involves administering to a nonhypercholesterolemic subject in need of such treatment a HMG-CoA reductase inhibitor that increases endothelial cell Nitric Oxide Synthase activity in an amount effective to increase endothelial cell Nitric Oxide Synthase activity in the tissue of the subject.

Therefore, because Liao actually teaches the increase of endothelial cell nitric oxide synthase activity, it teaches the opposite of what is recited in the Applicants' claims. Hence, Liao does not teach every element of the rejected claims and, consequently, does not anticipate the claimed invention. For this reason alone, this rejection may be withdrawn.

Additionally, the Applicants would like to draw the attention of the Office to the Court's ruling in SmithKline Beecham, wherein it was held that in order to anticipate a claimed invention a prior art disclosure must be enabling, such that one of ordinary skill in the art could practice the invention without undue experimentation. See SmithKline Beecham Corp. v. Apotex Corp., 403 F.3d 1331, 1342 (Fed. Cir. 2005).

The Applicants contend that given the disclosure set forth in Liao, one of ordinary skill in the art could not practice the Applicants' claimed invention without undue experimentation. One of skill in the art could not practice the Applicants' claimed invention without undue experimentation, in view of Liao, because Liao is directed to administering a HMG-CoA reductase inhibitor to upregulate endothelial cell NOS activity and thereby treating a disease condition.

However, the Applicants' claimed invention is based partially upon the discovery that HMG-CoA reductase inhibitors show efficacy both in (1) preventing the development of smooth muscle cell hyperplasia (including medial hypertrophy), and in (2) inducing apoptosis in diseased and hypertrophied vascular tissues. The Applicants' discovery is in sharp contrast to methods, such as those disclosed in Liao, which teach the administration of HMG-CoA reductase inhibitors to increase expression of NOS. As stated in the Applicants' specification at page 10, lines 9 to 24:

> "This discovery is in sharp contrast to earlier ideas postulating that HMG-CoA reductase inhibitors act to increase expression or activity of endothelial cell nitric oxide synthase (NOS), thereby relieving the symptoms of pulmonary hypertension or other vascular disorder by relaxing the vascular smooth muscle cells. Instead, the present applicants show that antiproliferative agents such as HMG-CoA reductase inhibitors are involved in direct resolution of the neointimal smooth muscle hyperplasia and medial hypertrophy that causes the vascular occlusion in disease states associated with lung proliferative vascular disorders. In fact, it is demonstrated herein that antiproliferative agents induce apoptosis of vascular smooth muscle cells, resulting in shrinkage of the tissue and direct resolution of the vascular occlusion. The decrease in vascular occlusion

that results is much greater than any vasodilation that could occur from the administration of a vasodilator, even in the presence of normal levels of eNOS."

Accordingly, due to the fact that Liao involves administering a HMG-CoA reductase inhibitor to upregulate endothelial cell NOS activity, the results of which have been questioned[1], and the Applicants' methods involve the administration of a HMG-CoA reductase inhibitor to reverse vascular occlusion by reversing neointimal hyperplasia, and thereby promoting the restoration of normal healthy endothelial cells, the Applicants contend that in view of the teachings of Liao, one of ordinary skill in the art could not practice the claimed invention without undue experimentation. Therefore, for this reason alone this rejection may be withdrawn.

In view of the above, the Applicants contend that Claims 1-10, 12, 19-22, 30-36 and 38-39 are not anticipated by Liao because Liao fails to teach all the elements of the rejected claims and/or is not enabled with respect to the Applicants' claimed invention. Consequently, the Applicants respectfully request that the 35 U.S.C. § 102(b) rejection be withdrawn.

Claim Rejections - 35 U.S.C. § 103

Claims 23-24 and 37 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Liao *et al. supra* or Nishimura *et al. supra*.

According to the MPEP § 706.02 (j), to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

Claims 23-24 ultimately depend from Claim 1. As set forth above, an element of Claim 1 is administering an amount of a HMG-CoA reductase inhibitor that is effective to reduce vascular occlusion in the pulmonary arteries but does not substantially increase endothelial cell nitric oxide synthase activity in the endothelial cells of the pulmonary arteries.

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[1] Reports concerning the role of NOS in pulmonary vascular diseases are contradictory. Berger *et al.* stated that it remains uncertain whether impaired endothelium-dependent vasorelaxation is associated with a decrease in NOS activity, and suggested that other alterations in endothelial cell metabolism may be primarily responsible for the impaired vasorelaxation. In short, these authors stated that impaired endothelial-dependent vasorelaxation may occur despite increased NOS activity. (Berger, R, et al. (2001) Am. J. Respir. Crit. Care Med. 163:1493-1499). See page 3, lines 6 to 11.

With respect to Liao, the Applicants contend that Liao does not teach or suggest this element because Liao actually teaches the increase of endothelial cell nitric oxide synthase activity. Additionally, as described above, Liao is not enabled with respect to the Applicants' claimed invention. Therefore, the Applicants contend that a *prima facie* case of obviousness has not been established because Liao fails to teach all the elements of the rejected claims and/or is not enabled. Consequently, the Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of Claims 23-24 be withdrawn.

With respect to Nishimura, the Applicants contend that a *prima facie* case of obviousness has not been established because, as described above, Nishimura cannot be used as prior art against the Applicants' claimed invention. Consequently, the Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of Claims 23-24 be withdrawn.

Claims 13 has been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Liao et al. *supra*.

Claim 13 depends from Claim 1. An element of Claim 1 is administering an amount of a HMG-CoA reductase inhibitor that is effective to reduce vascular occlusion in the pulmonary arteries but does not substantially increase endothelial cell nitric oxide synthase activity in the endothelial cells of the pulmonary arteries. The Applicants contend that a *prima facie* case of obviousness has not been established because Liao fails to teach this element of the rejected claims. Additionally, as described above, Liao is not enabled with respect to the Applicants' claimed invention. Consequently, the Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of Claim 13 be withdrawn.

CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-352.

Respectfully submitted,

BOZICEVIC, FIELD & FRANCIS LLP

Date: February 20, 2007

By: _____
Pamela J. Sherwood
Registration No. 36,677

Enclosure: Executed Declaration of Peter N. Kao Under 37 C.F.R. § 1.132 and MPEP 716.10

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